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SYNTHESIS, CHARACTERIZATION, ANTI-OXIDANT AND ANTICONVULSANT ACTIVITY OF SYNTHESIZED SCHIFF-BASES THROUGH STRUCTURE ACTIVITY RELATIONSHIP (SAR) STUDY AND ITS EFFECT ON BRAIN GABA LEVEL IN MICE

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ABSTRACT

Background: Three benzaldehyde derived Schiff-bases (**SH 1-3**) were synthesized by a condensation reaction from *o*-phenylenediamine with their respective benzaldehyde derivatives in absolute ethanolic solution under reflux reaction mixture for 6-8 hrs. The structural determinations of the synthesized Schiff-bases were confirmed by FT-IR and ^{1}H-NMR spectroscopy. Benzaldehyde derived Schiff-bases are well-known to possess potent antioxidant and anticonvulsant activities etc. In view of the importance of various benzaldehyde derivatives, the present investigation was undertaken which deals with the structure activity relationship (SAR) study and evaluation of the antioxidant and anticonvulsant activity of synthesized Schiff-bases in mice models.

Materials and Methods: DPPH scavenging activity was used to assess the antioxidant activity. Pentylenetetrazole (PTZ) seizure models were used to evaluate the anticonvulsion activity and biochemical evaluation by estimation of brain GABA level of synthesized compounds.

Results: In SAR study, the results revealed that the synthesized compounds **SH 3**, **SH 2** and **SH 1** at dose of 50 mg/kg show potent pharmacological activities like antioxidant and anticonvulsant activities respectively as compared to the control group at ($p<0.001$).

Conclusion: The significant results were showed by the synthesized compounds **SH 3**, **SH 2** and **SH 1** respectively in suitable and intermediate ranges which prompted us to study their other pharmacological activities like antiviral, antibacterial, anticancer and so on. Also, the results revealed that the synthesized compounds have some effects on benzodiazipines receptors and it might link with binding sites that altered the activity of GABA receptor complex. These observations suggested that the anticonvulsant activity of synthesized compounds could be due to the involvement of the GABAergic pathway since further studies

are require to exposed the underlying mechanism in detail.

INTRODUCTION

Schiff bases are the organic compounds having an imine functional group which have been formed by the condensation of primary amines with an aldehydes or ketones. Schiff base complexes especially the metal Schiff base complexes are well known catalysts and showed vital biological applications (Al Zoubi, Al-Hamdani et al. 2016). First time Hugo Schiff reported Schiff bases in 1864, which have been prepared usually by its own discovered method involving the condensation of an aldehyde or ketone (carbonyl compound) with an amine under different reaction conditions and solvents (Hameed, al-Rashida et al. 2017). Schiff bases of benzaldehyde derivatives are the effective organic compounds which holds vital biological and pharmacological activities including anti-inflammatory, anlagesic, antimicrobial, tuberculostatic, anticancer, antidepressant, anticonvulsant, anti-HIV, antileshmanial, insecticides and fungicides activities (Abdulghani and Hussain 2015). Free radicals have unpaired electrons that promote oxidative damage in the body and causes heart disease, diabetes mellitus and cancer. Antioxidants react with free radicals and inhibit oxidation of molecules as they have the ability to accept or donate electrons (Liguori, Russo et al. 2018). Isoxazole Schiffbase derivatives exhibited significant antioxidant activity (Ganji, Rambabu et al. 2018). Demetgul and Beyazit in 2018 synthesized chitosan-chromone schiff base derivatives and were found to possess significant antioxidant activity (Demetgül and Beyazit 2018). Epilepsy is common neurological disorder followed by periodic incidence of neuronal discharge, seizures, loss of consciousness and abnormal electrical activity in the brain. Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter and the decrease in GABA level cause epilepsy that mainly produced by reason of GABA synthesis inhibition or post-synaptic GABA receptor blockage (Murtaza, Akhtar et al. 2017). Various Schiff bases derivatives i.e. hydrazone Schiff base of isatin derivatives (Zlatkovic, Troter et al. 2018) and a series of quinazolinone derivatives (Abulkhair, El-Gamal et al. 2016) hold major anticonvulsant activities.

In view of the importance of various benzaldehyde derivatives, in this document we discuss synthesis of benzaldehyde derived Schiff bases and their potent antioxidant and anticonvulsant activities.

Materials and Methods

Chemicals and materials

Different solvents used in my research are distilled water, ethanol, methanol, *n*-hexane, normal saline and Tween 80 that's were purchased in Lahore (Pakistan) from Merck. The reactants such as *o*-phenylenediamine and aldehyde derivatives i.e. 4-nitrobenzaldehyde, 4-chlorobenzaldehyde and 4-dimethylbenzaldehyde were accepted as a kind gift from Chemistry Department at University of Azad Jammu and Kashmir. Diazepam (10 mg/2 ml), Pentylenetetrazole (PTZ), Vigabatrin (VGB), Ninhydrin and GABA were also used.

Instrumentation

The compounds were confirmed by ^{1}H-NMR spectra at 300 MHz through Bruker Avance spectrometer with an internal standard used as TMS (titramethyl silane). Parts per million (ppm) was recorded to point out the chemical shift values. Also IR Spectroscopy was obtained, for IR spectra Bio-Rad Merlin Fourier Transform Infra-Red spectrophotometer was used. Melting points of synthesized compounds were got in Barnstead electrothermal apparatus. TLC plates

(Merck 60 F_{254}) procured from Merck Darmstadt Germany were used to observed product formation under UV lamp.

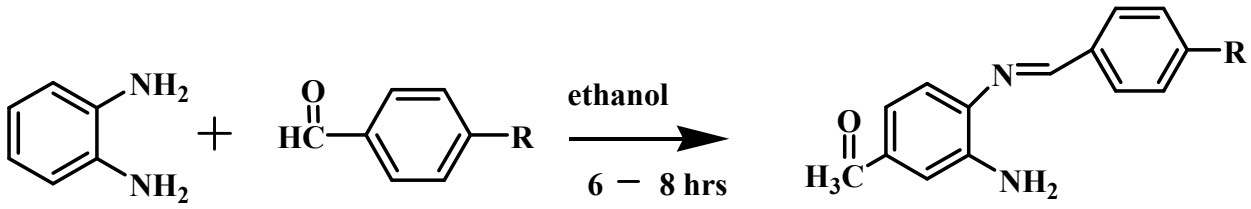
Animals used

Male albino mice weighting (20-25 grams) were procured from National Institute of Health Islamabad Pakistan. Pieces of soft wood like bedding were used to kept mice in cages and acclimatization period was provided under standard laboratory conditions. Animals were placed in a room having 12 hrs of light and dark cycle at control temperature and standard diet was supplied on the daily need base.

Methodology

Synthesis of Schiff bases (SH 1–3)

The synthesized benzaldehyde derived Schiff bases (**SH 1–3**) were prepared according to the reported protocols. A solution of the *o*-phenylenediamine (1 mmol) in absolute ethanol (10-15 mL) was slowly added to a solution of the aldehyde derivatives (1 mmol) in absolute ethanol and refluxed the reaction mixture for 6-8 hrs. For synthesis of **SH 1**, **SH 2** and **SH 3** compound 4-nitrobenzaldehyde, 4-chlorobenzaldehyde and 4-dimethylbenzaldehyde were taken respectively. After completion of reaction, the contents were cooled and precipitates were formed which collected by filtration, then washed several times with cold ethanol (Luo, Xia et al. 2017).



SH 1 = R = NO_2

SH 2 = R = Cl

SH 3 = R = $N(CH_3)_2$

Scheme 1: Synthesis of compounds (SH 1–3)

Pharmacological activities

Antioxidant activity

The antioxidant activity of synthesized Schiff bases were determined by the DPPH free radical scavenging method.

DPPH scavenging activity

The antioxidant activity of synthesized compounds was measured by making its stock solutions in methanol (1000 µg/ml). For preparing stock solutions, 10 mg of each compound dissolved in 10 ml of methanol. The prepared stock solutions were then diluted to different concentrations of 62.5, 125, 250, 500 and 1000 µg/ml. Same concentration was used for standard ascorbic acid. 2% methanolic solution of 1,1-diphenyl-2-picrylhydrazyl (DPPH) was made and 1 ml from this solution was added to each 1 ml of different concentrations of the tested synthesized compounds. The resultant concentrations of synthesized compounds were taken to dark area and incubated for 30 min. Blank solution was prepared by dissolving DPPH in methanol and spectrophotometer

was used to measured the absorbance at 517 nm. The antioxidant activity of tested synthesized compounds was calculated by the following formula (Schaich, Tian et al. 2015).

% inhibition of DPPH activity = A-B/A × 100

A represents absorbance of blank and B represents absorbance of test sample.

Anti-convulsion activity

Plexiglass apparatus was used in anti-convulsion model. All mice were divided into control, standard and three tests groups each containing six animals. The control group was treated with normal saline (10 ml/kg), the standard group was treated with diazepam (1 mg/kg, i.p) and three test groups were treated orally with synthesized compounds at a dose of 50 mg/kg body weight. Pentylenetetrazole was administered to each animal i.p at a dose of 80 mg/kg body weight to induced seizures in mice, thirty minutes after the treated compound dose and 15 minutes after diazepam treatment. A video camera was used to record the onset of clonic, tonic-clonic and duration of tonic-clonic convulsion immediately after pentylenetetrazole injection. The mortality was observed for the next 24 h. The test was performed according to the described method with slight modifications (Divar, Yeganeh et al. 2017).

Biochemical evaluation by estimation of brain GABA

All mice were divided into control, normal, standard and three tests groups each containing six animals. The control group was treated with normal saline and PTZ, the normal group was treated with normal saline (10 ml/kg) only, the standard group was treated with PTZ and Vegabatrin (100 mg/kg, i.p) and three tests groups were treated orally with synthesized compounds at a dose of 50 mg/kg body weight along with PTZ injection. Pentylenetetrazole was administered to animals i.p at a dose of 80 mg/kg body weight to induced seizures in mice, thirty minutes after the treated compound dose and 15 minutes after vegabatrin treatment. Mice were euthanized as soon as onset of convulsions occurs after PTZ treatment. Brains were isolated, homogenized and then dissolved in 8 ml of 75% alcohol with 8 ml of 0.1N HCl. Brains homogenate were kept in refrigerator for 1 hr and centrifuged at 16000 rpm for 10 min. Supernatant of the contents were collected in petridishes and lower layers precipitates were discarded. Contents in petridishes were evaporated to dryness at room temperature. To the dry mass 3 ml water and 7 ml chloroform were added to each petridish and recentrifuged at 2000 rpm for 20 min. Upper layer containing GABA (2 ml) was separated and 10 µl spot of it was applied on Whatman paper (No. 41). By dipping the lower portion of paper in beaker containing solvents served as mobile phase i.e. butanol (50 ml), acetic acid (12 ml) and water (60 ml) for half an hour and paper chromatogram was developed. The paper was dried and then spread with 0.2% ninhydrin solution in 95% ethanol. Blue color spot appeared on paper while drying it and was cut, then heated with 2 ml ninhydrin solution. Water (5 ml) was added to the solution and kept for 1 h. Supernatant was collected and absorbance was measured by spectrophotometer at 571 nm. The test was performed according to the described method with slight modifications (Tamboli, Rub et al. 2012).

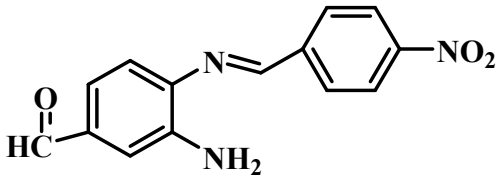
Statistical analysis

Means and standard error means (SEMs) for the data were calculated by using Excel, then all the statistical analysis were determined by using one way ANOVA followed by Dunnet's Multiple Comparison Test in GraphPad Prism.

RESULTS AND DISCUSSION

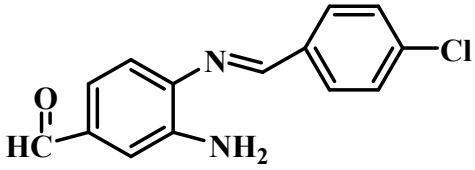
Synthesis

The synthesized benzaldehyde derived Schiff bases were prepared by adding *o*-phenylenediamine to their respective aldehydes solution which gave rise to three benzaldehyde derived Schiff bases. The synthesized compounds are shown in figure 1 – 3.



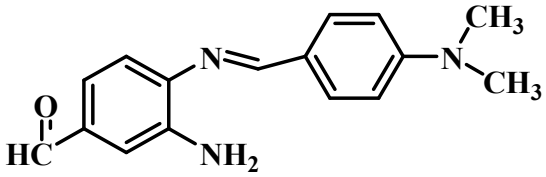
(*E*)-4-(4-nitrobenzylideneamino)-3-aminobenzaldehyde

Figure 1: Compound SH 1



(*E*)-4-(4-chlorobenzylideneamino)-3-aminobenzaldehyde

Figure 2: Compound SH 2



(*E*)-4-(4-(dimethylamino)benzylideneamino)-3-aminobenzaldehyde

Figure 3: Compound SH 3

Analytical details

The structural elucidations of the compounds were based on their physical data as given below.

Table 1: Physical data of synthesized Schiff bases (SH 1–3).

Name	Mol For	Mol. Wt	App	Yeild	R.f	m.p.
SH 1	$C_{13}H_{11}N_3O_2$	241.25	Brown color powder	58.3%	0.63	299-301 ºC
SH 2	$C_{13}H_{11}ClN_2$	230.06	Orange color powder	67.1%	0.71	282-284 ºC
SH 3	$C_{15}H_{17}N_3$	239.14	Yellow color powder	75.6%	0.68	131-133 ºC

Characterization of Schiff bases

The synthesized compounds were characterized by their respective spectral data as mentioned below.

Compound SH 1:

IR (KBr) cm-1: 3459, 3368 (NH_2), 1583 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) ppm: 8.64 (s, 1H), 8.32 (d, 2H), 8.06 (d, 2H), 7.15-7.11 (m, 2H), 6.82-6.74 (m, 2H), 4.39 (br. s, 2H); Anal. calcd: C 64.72, H 4.60, N 17.42. Found: C 64.59, H 4.71, N 17.49.

Compound SH 2:

IR (KBr) cm-1: 3461, 3371 (NH_2), 1581 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) ppm: 8.53 (s, 1H), 7.81 (d, 2H), 7.49 (d, 2H), 7.21 (d, 2H), 6.81 (t, 2H), 4.33 (br. s, 2H); Anal. calcd: C 67.68, H 4.81, N 12.14. Found: C 68.09, H 4.69, N 11.90.

Compound SH 3:
IR (KBr) cm-1: 3463, 3369 (NH_2), 1589 (C=N); ^1H NMR (300 MHz, $CDCl_3$) ppm: 8.55 (s, 1H), 7.81 (d, 2H), 7.16-6.88 (m, 2H), 6.81 (d, 2H), 6.77 (d, 2H), 4.21 (br. s, 2H, NH_2), 2.91 (s, 6H, CH_3); Anal. calcd: C 75.28, H 7.16, N 17.56. Found: C 75.59, H 7.25, N 17.49.

Pharmacological activities

Antioxidant activity

The synthesized Schiff bases **SH 1**, **SH 2** and **SH 3** were screened for their possible antioxidant activity in DPPH free radicals scavenging method. In DPPH activity ascorbic acid was used as a positive control. The IC_{50} values for each compounds were calculated. The results reveals that the compounds **SH 3**, **SH 2** and **SH 1** have good antioxidant activity respectively when compared to their respective taken control. However, the compound **SH 3** showed comparatively best IC_{50} value.

Table 2: DPPH scavenging activity of synthesized Schiff bases.

Test Sample	Sample concentration (µg/ml)	% Activity shown	IC_{50} (µg/ml)
SH 1	1000 500 250 125 62.5	$61.12 \pm 2.16^{**}$ $55.24 \pm 3.38^{**}$ 49.54 ± 1.29^{ns} 44.43 ± 3.40^{ns} $35.73 \pm 4.17^{**}$	427.391
SH 2	1000 500 250 125 62.5	65.82 ± 2.56^{ns} 63.21 ± 1.64^{ns} 55.77 ± 2.23^{ns} 45.21 ± 4.32^{ns} 39.90 ± 1.41^{ns}	238.8
SH 3	1000 500 250 125 62.5	66.51 ± 2.72^{ns} 62.44 ± 4.53^{ns} 56.87 ± 2.15^{ns} 45.32 ± 2.18^{ns} $39.54 \pm 2.27^{*}$	230.8
Control (Ascorbic acid)	1000 500 250 125 62.5	75.20 ± 1.46 69.16 ± 2.55 57.02 ± 1.74 51.07 ± 1.13 49.36 ± 1.22	24.29

All values expressed as mean ± S.E.M (standard error mean) where n=6, ns= not significant, $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ when compared with the control by using two way ANOVA followed by Bonferroni post test.

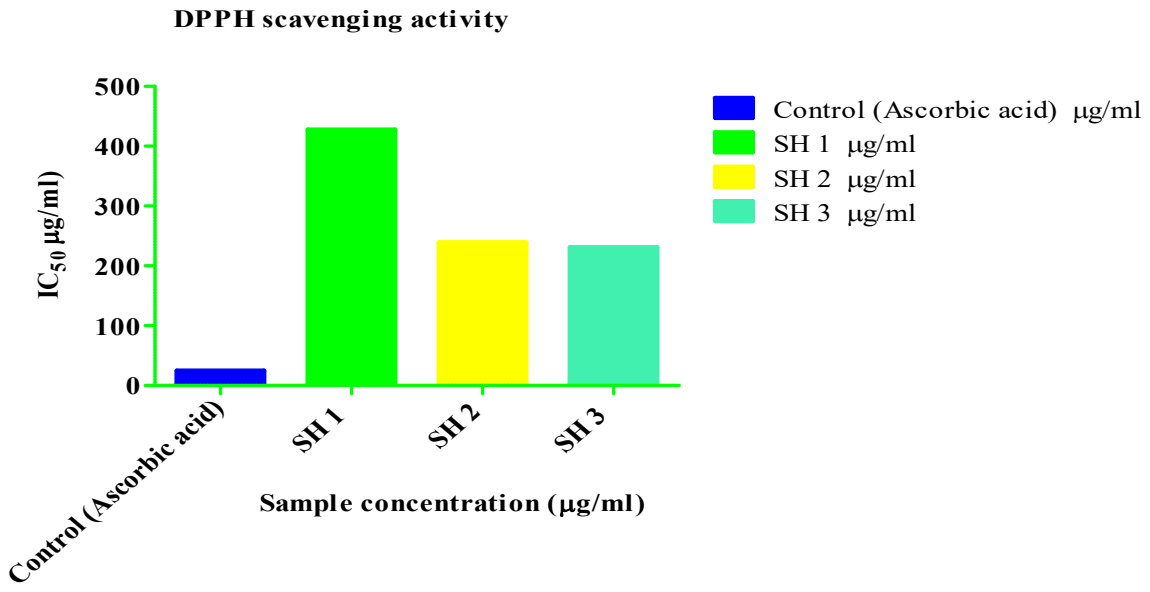


Figure 4: DPPH free radicals scavenging activity of synthesized Schiff bases against IC_{50}.

Anti-convulsion activity

All mice were divided into control, standard and three tests groups each containing six animals. The control group was treated with normal saline (10 ml/kg), the standard group was treated with diazepam (1 mg/kg, i.p) and three test groups were treated orally with synthesized compounds at a dose of 50 mg/kg body weight. Pentylenetetrazole was administered to each animal i.p at a dose of 80 mg/kg body weight to induced seizures in mice, thirty minutes after the treated compound dose and 15 minutes after diazepam treatment. The compounds **SH 3**, **SH 2** and **SH 1** significantly prolonged the onset of clonic and tonic-clonic convulsion respectively as compared to control group, whereas significant reduction showed by these tested compounds respectively in duration of tonic-clonic convulsion as compared to the control group. The compound **SH 1** showed 16.7% mortality, while no mortality exhibited by the compounds **SH 2** and **SH 3** when compared to the control group. However, in diazepam treated group no convulsion was take place and 100% protection occurred from PTZ induced convulsion and mortality.

Table 3: Effects of synthesized Schiff bases on anti-convulsion activity in mice.

Treatment	Dose (mg/kg)	Onset of clonic convulsion (sec/30min)	Onset of tonic-clonic convulsion (sec/30min)	Duration of tonic-clonic Convulsion(sec/30min)	Mortality (%)
Control (PTZ+ NS)	80	48 ± 1.847	232.5 ± 4.692	40.332 ± 3.64	100
PTZ + Diazepam	1	–***	–***	–***	0
PTZ + SH 1	50	57.333 ± 2.19*	276.866 ± 3.56***	27.024 ± 2.428***	16.7
PTZ + SH 2	50	71.62 ± 2.648***	291.17 ± 4.919***	20.333 ± 1.826***	0
PTZ + SH 3	50	95.528 ±	327.833 ±	12.17 ± 1.061***	0

		3.727***	5.618***		

All values expressed as mean ± S.E.M (standard error mean) where n=6, ns= not significant, *p<0.05, **p<0.01 and ***p<0.001 when compared with the control by using one way ANOVA followed by Dunnet's Multiple Comparison Test. The (–) sign represents that there was no convulsion take place in diazepam treated group.

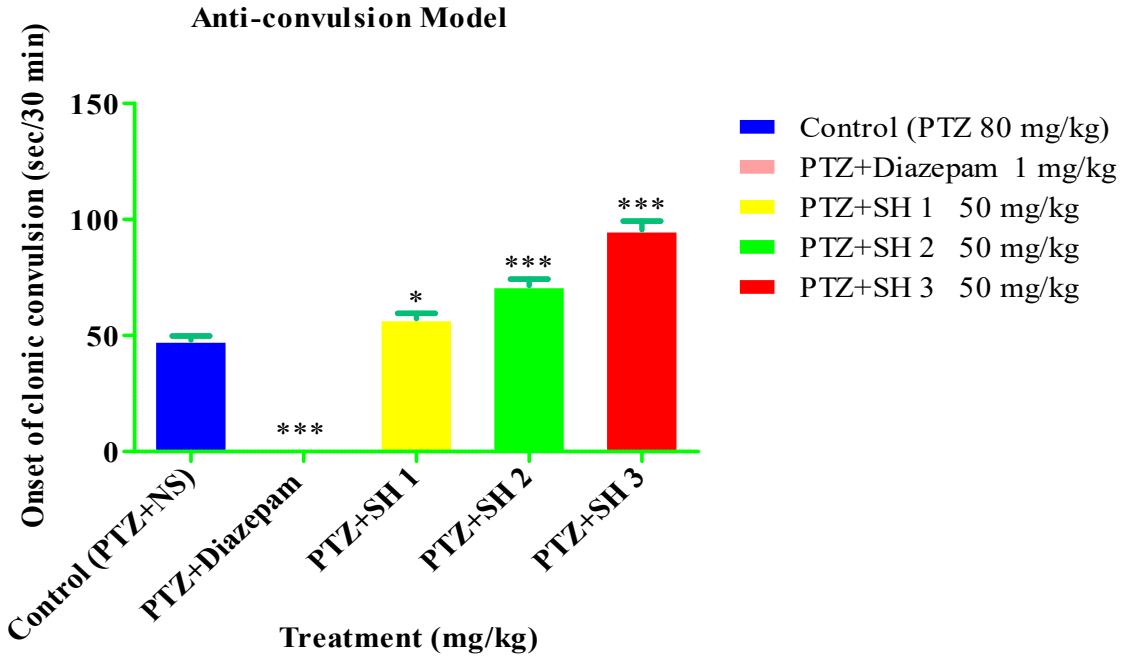


Figure 5: The effects of synthesized Schiff bases on the onset of clonic convulsion. Bars represent mean ± S.E.M from six mice.

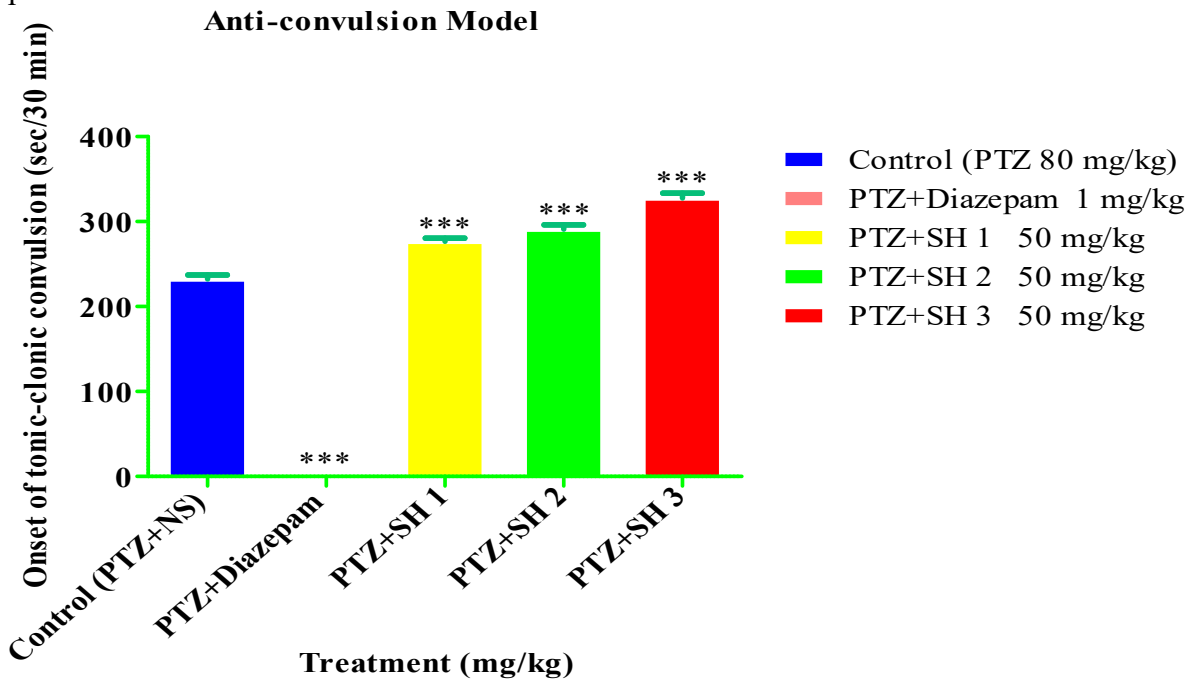


Figure 6: The effects of synthesized Schiff bases on the onset of tonic-clonic convulsion. Bars represent mean ± S.E.M from six mice.

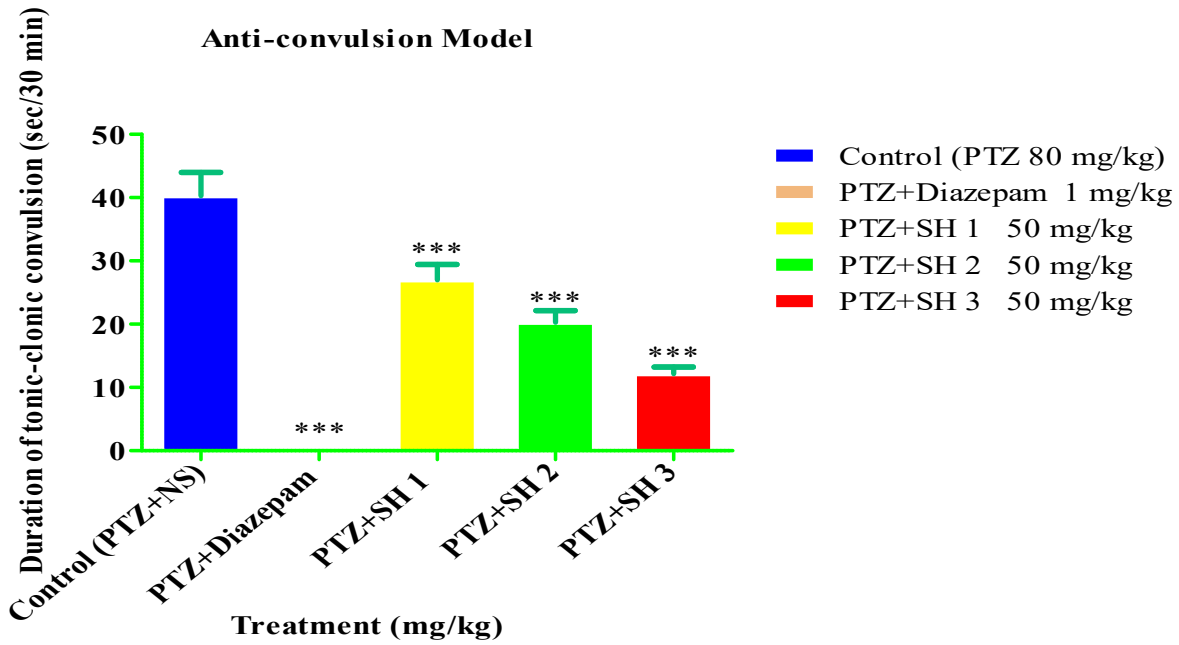


Figure 7: The effects of synthesized Schiff bases on the duration of tonic-clonic convulsion. Bars represent mean ± S.E.M from six mice.

Biochemical evaluation by estimation of brain GABA

All mice were divided into control, normal, standard and three tests groups each containing six animals. The control group was treated with normal saline and PTZ, the normal group was treated with normal saline (10 ml/kg) only, the standard group was treated with PTZ and Vegabatrin (100 mg/kg, i.p) and three tests groups were treated orally with synthesized compounds at a dose of 50 mg/kg body weight along with PTZ injection. Pentylenetetrazole was administered to animals i.p at a dose of 80 mg/kg body weight to induced seizures in mice, thirty minutes after the treated compound dose and 15 minutes after vegabatrin treatment. PTZ produced significant reduction in the level of GABA in mice brain homogenate as compared to normal group. The compounds **SH 3**, **SH 2** and **SH 1** showed significant improvement in GABA level respectively when compared to the control group. However, vegabatrin exhibited significant increase in the level of GABA.

Table 4: Effects of synthesized Schiff bases on GABA estimation in mice.

Treatment	Dose (mg/kg)	GABA (ng/mg of brain tissue)
Control (PTZ + NS)	80	335.833 ± 4.822
Normal	Normal saline (10ml/kg)	415.694 ± 6.410***
PTZ + Vegabatrin	100	522.17 ± 5.836***
PTZ + SH 1	50	377.04 ± 4.640***
PTZ + SH 2	50	409.817 ± 5.308***
PTZ + SH 3	50	453.25 ± 3.648***

All values expressed as mean ± S.E.M (standard error mean) where n=6, ns= not significant, *p<0.05, **p<0.01 and ***p<0.001 when compared with the control by using one way ANOVA followed by Dunnet's Multiple Comparison Test.

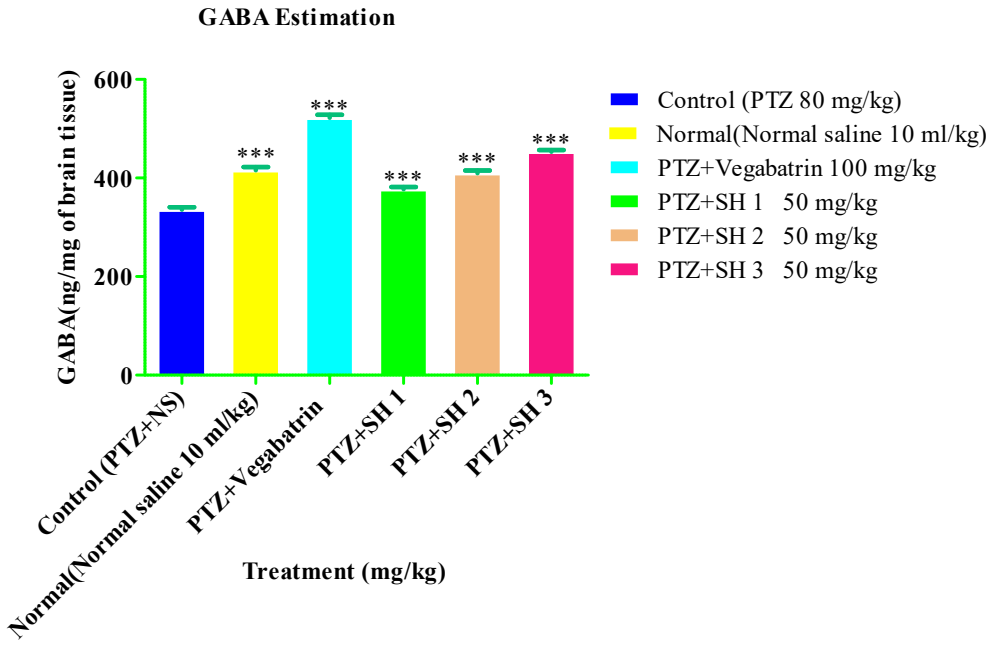


Figure 8: The effects of synthesized Schiff bases on GABA level in brain tissue. Bars represent mean ± S.E.M from six mice.

Discussion

Schiff bases are the important class of organic compounds which contain the azomethine group (−C═N−) and have varieties of applications in industrial, pharmaceutical, clinical, pharmacological and biological areas. Schiff bases have been the topic of interest for synthetic and medicinal chemists due to their facile synthesis, prominent flexibility and stability and metal complexes formation. Due to these properties they have numerous applications i.e. in manufacturing of certain dyes, bacteriocides, pesticides, fungicides and insecticides (Mesbah, Douadi et al. 2018). Plants mainly high phenolic contents, vegetables and fruits are the natural sources of antioxidants containing less side effects, while many synthetic antioxidants have been synthesized which possess various side effects. Vitamin C or ascorbic acid is a natural antioxidant and commonly used in DPPH activity. DPPH is the method of measuring free radicals scavenging ability and has been reported for their cheap, accurate and facile usage. IC_{50} is the minimum effective concentration of test solution that can reduce the amount of free radicals by 50 percent. Test solution having low value of IC_{50}, be the greater antioxidant potential (Retnaningtyas and Setiadi 2017). In our study the IC_{50} values for DPPH free radicals scavenging activity were calculated. The results demonstrated that the compounds **SH 3**, **SH 2** and **SH 1** have good antioxidant activity respectively when compared with the control. However, the compound **SH 3** showed comparatively best IC_{50} value **(Table 2)**. In convulsion model the PTZ induced seizures in mice by reduction in the GABA level. GABA play a prominent inhibitory role in the CNS of mammals and convulsion is followed by the decreased in GABA activity as GABA enhances the chloride ions conductance (Motevalian, Mehrzadi et al. 2017). In our study the synthesized compounds **SH 3**, **SH 2** and **SH 1** showed a significant reduction in duration of seizures and also increased the onset of seizures respectively **(Table 3)**. The results revealed that the synthesized compounds have some effects on benzodiazipines receptors and it might link with binding sites that alters the activity of GABA receptor complex. Also, GABA concentrations in mice brain were measured and the results showed that vegabatrin significantly increased the GABA level. As vegabatrin inhibit GABA transaminase thus prevent the

breakdown of GABA and exhibited good antiseizures effects (Zhang, McDaniel et al. 2013). In our study the PTZ significantly reduced the GABA level in the mice brain whereas the synthesized compounds **SH 3**, **SH 2** and **SH 1** showed significant enhanced in the GABA level respectively **(Table 4)**. These observations recommended that the anticonvulsant activity of synthesized compounds could be due to the involvement of the GABAergic pathway.

Conclusion

The benzaldehyde derived Schiff bases **SH 1**, **SH 2** and **SH 3** were synthesized and studied for the antioxidant and anticonvulsant activities. The special focus in this study was intended for the screening of pharmacological behaviors of these synthesized Schiff bases. The compound **SH 1** was found to possess poor pharmacological effects i.e. antioxidant and anticonvulsant activities while the compounds **SH 2** and **SH 3** showed significant pharmacological results which further requires to be studied for their other pharmacological activities like antiviral, antibacterial, anticancer and so on.

The compounds possess significant antioxidant activity. The anticonvulsant effect was evaluated by PTZ model and also in GABA isolation and estimation technique. The fruitful results were showed by the synthesized compounds in suitable and intermediate ranges. Also, the results revealed that the synthesized compounds have some effects on benzodiazipines receptors and it might link with binding sites that altered the activity of GABA receptor complex. These observations suggested that the anticonvulsant activity of synthesized compounds could be due to the involvement of the GABAergic pathway.

This study will clear the way for researchers in future and further studies are require to exposed the underlying mechanism in detail.

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